Synthesis of Some Bioactive Nitrogen Rich Heterocycles

Synopsis

of the Ph.D. Thesis to be submitted to the

MANGALORE UNIVERSITY

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

IN

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By

Mr. Vishwa B. Das

DEPARTMENT OF CHEMISTRY

MANGALORE UNIVERSITY

MANGALAGANGOTHRI-574 199

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Title of the Thesis: Synthesis of Some Bioactive Nitrogen Rich Heterocycles

Name of the Candidate: Mr. Vishwa B.Das

Name of the Guide: Dr. Boja Poojary

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Place of Work: Department of Chemistry
Mangalore University
Mangalagangothri-574 199
Karnataka. India.

Synopsis

Heterocyclic compounds are the class of cyclic organic compounds those having at least one heteroatom (*i.e.,* atom other than carbon) in the cyclic ring system. In a heterocyclic compound, the cyclic component indicates the presence of at least one ring structure, while the prefix hetero suggests the non-carbon atoms or heteroatoms, in the ring. Heterocycles and their derivatives play a pivotal role in natural products and synthetic organic chemistry. Isolation, biochemical synthesis and investigation of biological properties of diverse heterocycles have attracted both organic and medicinal chemists[1]. Heterocyclic compounds are found in nature in large quantities and are essential to life; they are fundamental to the metabolism of every living cell. Purines and pyrimidines are examples of heterocyclic bases that make up DNA, the genetic material. About 65% of the literature on organic chemistry is devoted to heterocyclic compounds, which are the focus of heterocyclic chemistry[2]. Several pharmacologically active heterocyclic compounds both synthetic and natural are used in therapeutics.

Modern medicinal chemistry is heading in the direction of developing innovative small molecules that have the ability to specifically block certain receptors in cancer cells. In recent years, much attention has been paid to the synthesis of fused systems based on thiazole and 1,2,4-triazole. There have been numerous reports of synthetic small molecules from various heterocyclic systems that have an impact on carcinogenesis and a few of them are currently undergoing research in clinical trials[3]. Due to the properties that fluorine confers on compounds and the potential biological activity it can produce, fluorine is now recognized as an indispensable tool for medicinal chemists. Since fluorine is the most electronegative element, integrating it into a drug candidate changes its electronic effects, which can also affect the characteristics of nearby functional groups. It can also have steric effects, changing the shape of the molecule. In addition, its rarity in nature makes it less likely to be broken down by naturally occurring enzymes, which can aid in increasing the metabolic stability of a medication[4-6]. A vast array of therapeutically intriguing drug candidates with antibacterial[7], anti-inflammatory[8], analgesic[9] and anticancer properties[10,11] have incorporated a significant number of 1,2,4-triazoles. The Schiff bases of 1,2,4-triazoles have a wide range of biological activities. Schiff bases, for instance, that originate from

3-substituted-4-amino-5-mercapto-1,2,4-triazoles possess antidepressant, analgesic, antibacterial and anti-inflammatory properties[12].

Studies on heterocyclic compounds containing bridgehead nitrogen atoms, particularly those holding triazolo[3,4-*b*][1,3,4]thiadiazine derivatives have received much interest because of their wide variety of applications, especially in the medicinal field. 1,2,4-Triazoles are found in a wide range of pharmaceutical drugs including antibacterial, antifungal, anti-inflammatory[13], antiviral[14], anticonvulsant[15] and anticancer[16]. 1,2,4-Triazoles display a diversity of biological applications such as tubulin polymerization inhibitors[17], fungistatic activities[18], DNA intercalators[19], GABAA1 and GABAA4 receptors[20], monoamine oxidase A and B inhibitors[21]. Triazolothiadiazines are little studied representatives of the bridgehead nitrogen atom class of compounds. Triazolo[3,4-*b*][1,3,4]thiadiazines are used as antimicrobial agents[22], anticonvulsant, CNS-depressant agents[23], pyruvate kinase[24], aromatase inhibitors[25], anti-coronavirus and antitumor activity[26].

Nitrogen-containing compounds, such as oxadiazoles, are privileged scaffolds for both medicinal and industrial fields[27]. They can function as flat aromatic linkers, pharmacophore components or moieties that modulate molecular properties[28]. Moreover, 1,3,4-oxadiazole heterocycles are effective bioisosteres of amides and esters and they can significantly enhance hydrogen-bonding interactions with receptors[29]. Within drug discovery and development, a number of compounds containing oxadiazole moiety are commercially used as drug such as Tiodazosin used as α_1-adrenergic receptor antagonist[30] and Fenadiazole used as a hypnotic drug[31] *etc*. 1,3,4-Oxadiazole-containing derivatives are used as DHFR inhibitors[32], γ-glutamylcysteine synthetase inhibitors[33], tubulin polymerization inhibitors[34], histone deacetylases inhibitors[35], DNA intercalative topo II inhibitors[36], thymidylate synthase inhibitors[37] and lipoxygenase inhibitors[38]. They are also known to possess various biological activities such as antimicrobial[39], antioxidant[40], neuraminidase inhibitors[41], α-glucosidase inhibitors[42], antiurease[43], etc.

1,3,4-Oxadiazole containing 1,2,3-triazole conjugates have also been reported and screened for anticancer activity. 1,3,4-oxadiazole-1,2,3-triazole conjugates are used as anticancer agents[44-47], α-glucosidase inhibitiors[48], anti-AChE agents[49] and GSK-3β

inhibitors[50]. A number of 1,2,3-triazole derivatives have also previously been used in clinical trials to treat cancer, making it a valuable building block in the search for new anticancer drugs. The 1,2,3-triazole framework can be hybridized with different anticancer pharmacophores to potentially give an effective therapeutic intervention for the treatment of cancer[51].

Synthesis of 1,2,3-triazole-embedded hydrazones and their efficiency in various biological fields have been reported in the literature. 1,2,3-Triazole-embedded hydrazones have a wide range of medicinal applications such as α-glycosidase inhibiton[52], antioxidant[53], antibacterial[54] and anticancer agents[55-57].

The aforementioned heterocyclic compounds have numerous biological applications and their biocompatibility makes them ideal for study. The objective of this work is to explore the biological applications of various heterocyclic derivatives as well as to develop synthetic techniques for obtaining them. The thesis entitled 'Synthesis of Some Bioactive Nitrogen Rich Heterocycles' has been divided into the following six chapters.

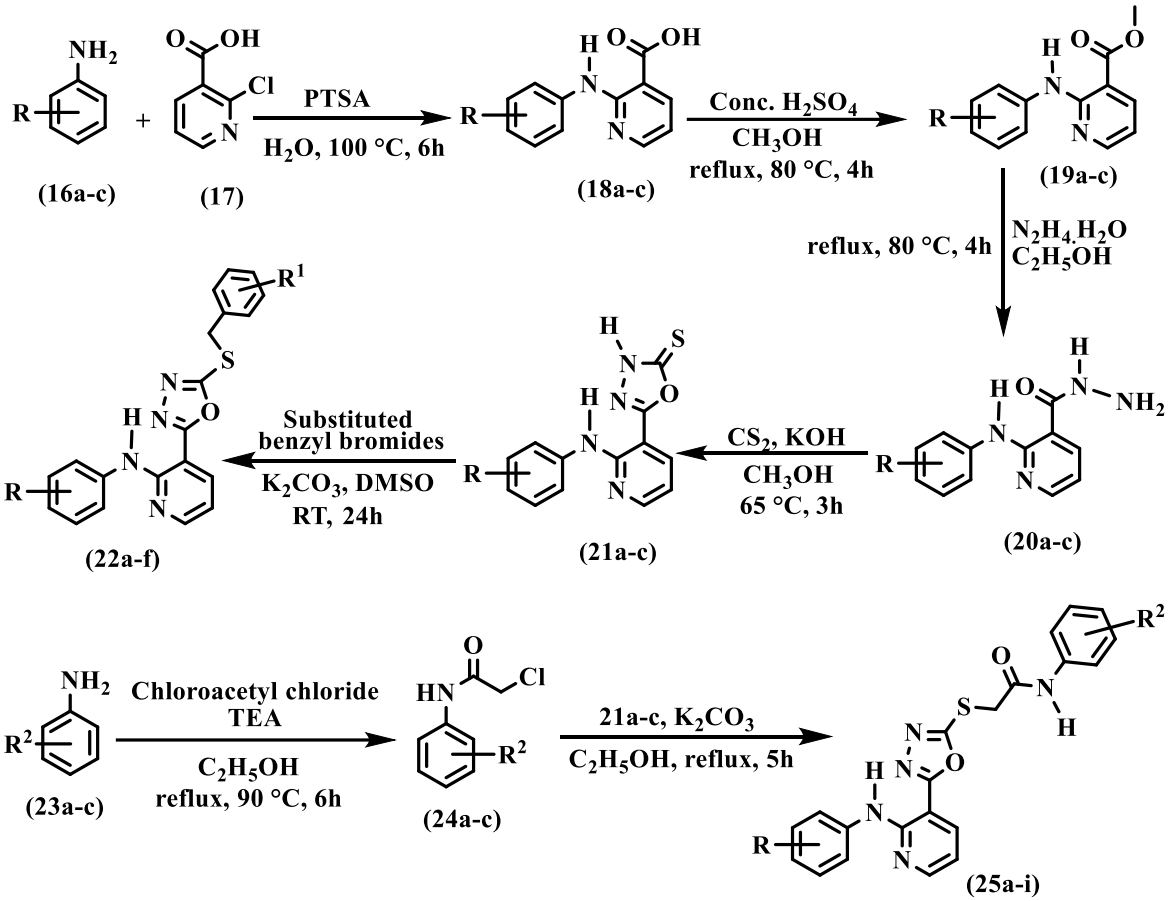
Chapter 1: A brief review on some simple and fused bioactive heterocyclic compounds

This chapter serves as an introduction, providing a brief overview on the synthesis and applications of several five and six-membered simple and fused heterocyclic derivatives found in publications in chemical literature until the year 2023. It focuses exclusively on the methods for synthesizing some heterocyclic compounds and the biological uses of those compounds.

Chapter 2: Synthesis and biological evaluation of *S*-alkylated 1,3,4-oxadiazoles containing arylaminopyridyl moiety

The synthetic pathway for the target compounds, *S*-alkylated 1,3,4-oxadiazole derivatives **(22a-f)** and **(25a-i)** is outlined in **Scheme 2.1**. Initially, substituted anilines **(16a-c)** are reacted with 2-chloronicotinic acid **(17)** to obtain 2-arylaminonicotinic acids (**18a-c**), which on esterification followed by hydrazenolysis yielded 2-arylaminonicotinohydrazides (**20a-c**). The resulting hydrazides are then cyclized with carbon disulphide in alkaline medium to get 5-(2-arylaminopyridin-3-yl)-1,3,4-

oxadiazole-2-thiones (**21a-c**). The intended *S*-alkylated compounds (**22a-f**) are synthesized by reacting the intermediate thiones (**21a-c**) with different substituted benzyl bromides in DMSO at room temperature while using potassium bicarbonate as the base. Meanwhile, substituted anilines (**23a-c**) were treated with chloroacetyl chloride to obtain chloro-(*N*-aryl)acetamides (**24a-c**) which on further reaction with intermediate (**21a-c)** afforded the second series of *S*-alkylated derivatives (**25a-i**). All synthesized *S*-alkylated derivatives were characterized by elemental analyses, FT-IR, $^{1}H/^{13}C$ NMR and Mass spectral techniques.



Where, **R** = 3-Cl-4-F, 4-F, 2-CH_3-5-NO_2; **R^1** = 4-Cl, 3-Cl-4-F, 4-NO_2, 2-oxo-2*H*-chromen-4-yl; **R^2** = 4-Cl, 2,4-$(Cl)_2$, 4-OCH_3.

Scheme 2.1: Synthetic pathway for the *S*-alkylated 1,3,4-oxadiazole hybrids **(22a-f)** and **(25a-i)**

The anticancer activity profile of the synthesized *S*-alkylated compounds is determined using MTT assay against the MCF-7 cancer cell line. The majority of the compounds

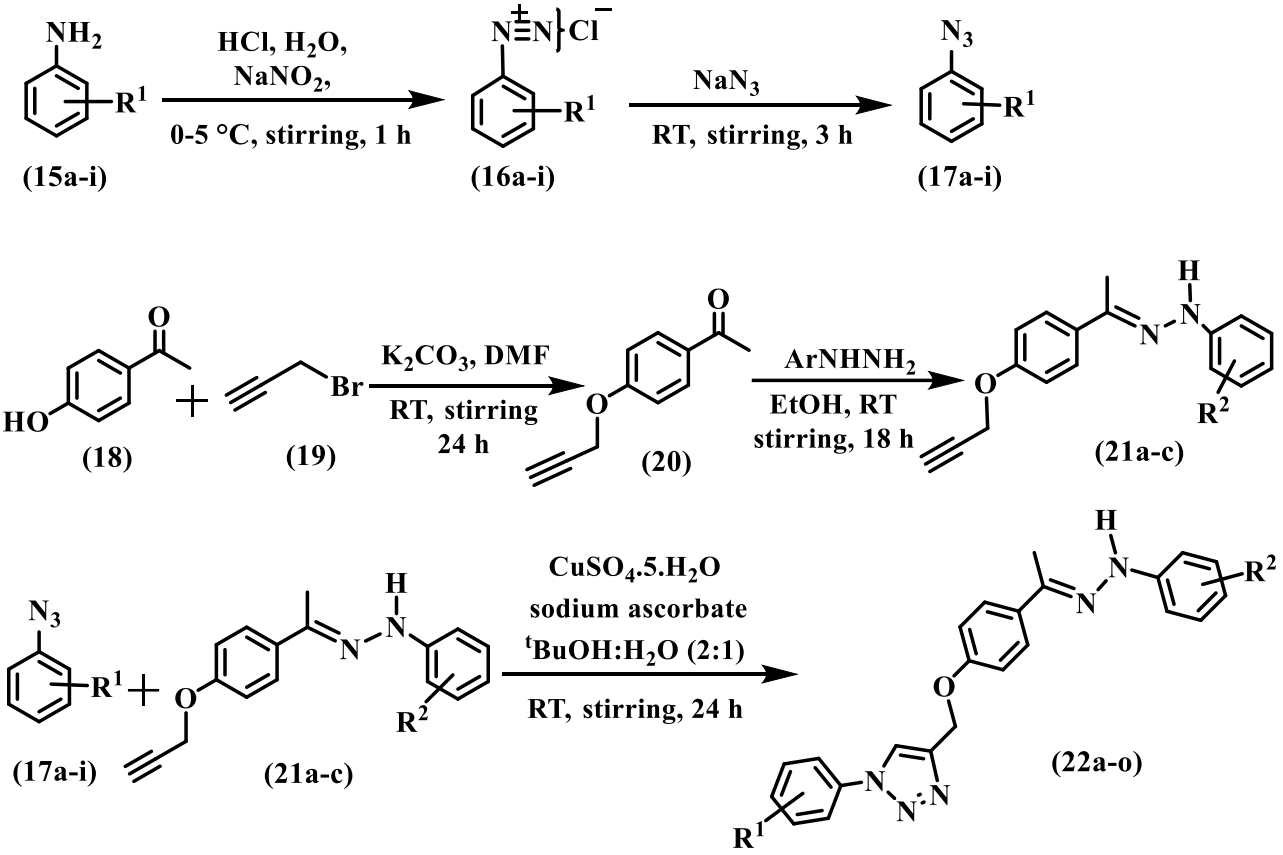
showed dose-dependent cytotoxicity at the stipulated time point studied. Two of the active compounds **22e** and **25d** are selected to analyse for their effect on nuclear morphology. Staining with DAPI showed visible signs of putative fragmentation of the cell nucleus post-treatment with the selected compounds. The anti-inflammatory and antioxidant properties of the synthesized *S*-alkylated compounds are evaluated, where compounds **25f, 25g** and **25h** displayed significant potency for antioxidant and anti-inflammatory activity. Molecular docking studies are carried out on all the synthesized molecules with crystal human estrogenic receptor alpha ligand-binding domain in complex with 4-hydroxytamoxifen, where compounds **22e, 25d** and **25c** showed good binding affinities with the target protein, human estrogenic receptor.

Chapter 3: Synthesis, anticancer evaluation and molecular docking studies of 1,2,3-triazole embedded hydrazones

This chapter describes the synthesis and characterization of some 1,2,3-triazole-embedded hydrazones followed by their anticancer evaluation and *in silico* molecular docking studies. The target compounds (**22a-o**) are synthesized as illustrated in **Scheme 3.1**. Substituted anilines (**15a-j**) are taken as starting materials which were diazotized followed by treatment with sodium azide to get respective azido intermediates (**17a-j**). Meanwhile, 4-hydroxyacetophenone (**18**) is reacted with propargyl bromide (**19**) to get the corresponding terminal alkyne (**20**). Further, intermediate (**20**) is reacted with substituted phenyl hydrazines to yield hydrazone intermediates (**21a-c**). The target compounds (**22a-o**) are then synthesized by the 1,3-dipolar cycloaddition reactions between aryl azides (**17a-j**) and intermediate hydrazones (**21a-c**). The structures of the synthesized compounds are confirmed on the basis of elemental analyses, FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

The anticancer activity of the synthesized derivatives (**22a-o**) is determined using MTT assay against the MCF-7 cancer cell line. The compound **22h** showed excellent cytotoxicity with an IC_{50} value of 0.9 µg/mL which is better than the standard drug etoposide and the rest of the synthesized derivatives exhibited moderate to good cytotoxic potential. The *in silico* molecular docking investigations verified that the

synthesized compounds demonstrated strong binding interactions with the target HER2 protein.



R^1 = H, 4-F, 4-Br, 2,4-Cl_2, 4-NO_2, 3-Cl-4-F, 2,4-$(CH_3)_2$, 2-CH_3-5-NO_2, 2,4,5-Cl_3; R^2 = H, 4-Cl, 4-Br.

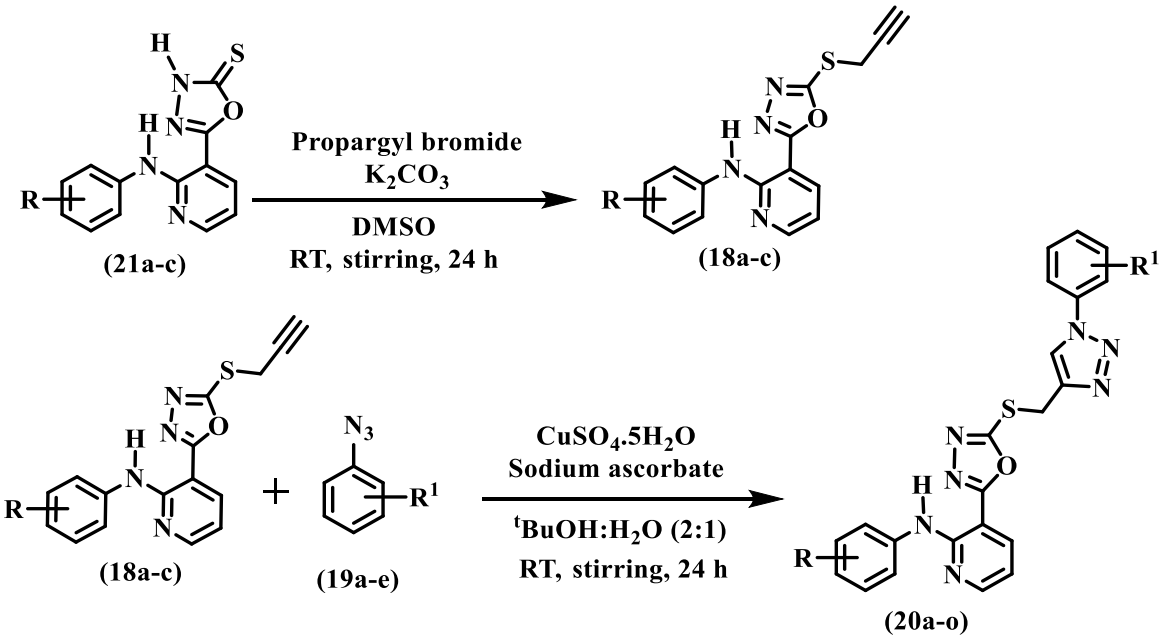
Scheme 3.1: Synthetic pathway for the 1,2,3-triazole-embedded hydrazones **(22a-o)**

Chapter 4: Synthesis and anticancer evaluation of some novel pyridine linked 1,2,3-triazol-4-yl-1,3,4-oxadiazole conjugates and their *in silico* molecular docking studies

A new series of pyridine linked 1,2,3-triazol-4-yl-1,3,4-oxadiazole conjugates is designed and synthesized as illustrated in **Scheme 4.1**. The new intermediates, 5-(2-arylaminopyridin-3-yl)-1,3,4-oxadiazole-2-thiones (**21a-c)** are synthesized from substituted anilines and 2-chloronicotinic acid as described in **Scheme 2.1** of **Chapter-2.** The reaction of these intermediates (**21a-c)** with propargyl bromide in the presence of potassium carbonate in DMSO at room temperature produced the corresponding

terminal alkynes of oxadiazoles (**18a-c**). The Click reaction between the resulting oxadiazole-terminal alkynes (**18a-c)** and substituted phenyl azides (**19a-e**) synthesized from the substituted anilines by diazotisation followed by nucleophilic substitution with azide ion afforded the pyridine-linked 1,2,3-triazol-4-yl-1,3,4-oxadiazole conjugates (**20a-o**). The structures of the synthesized compounds were confirmed on the basis of elemental analyses, FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

The synthesized derivatives were evaluated for their *in vitro* cytotoxicity against A549, Hep G2 and PC-3 cancer cell lines through a concentration range of 10-100 µM. Compounds **20b**, **20c, 20f** and **20k** showed excellent IC_{50} values against the tested cancer cell lines. Against A549 cells, the active compounds **20c** and **20f** greatly reduced the ability of single cells to form numerous colonies in a colony formation assay. Additionally, a wound healing assay was conducted on A549 cells where the active compounds **20c** and **20f** inhibited wound closure in a time-dependent manner, indicating their ability to hinder cell migration and gap closure. The *in silico* molecular docking studies of the synthesized derivatives showed good binding affinity towards the active binding site of the mTOR kinase structure of the target protein PDB:4JSV.

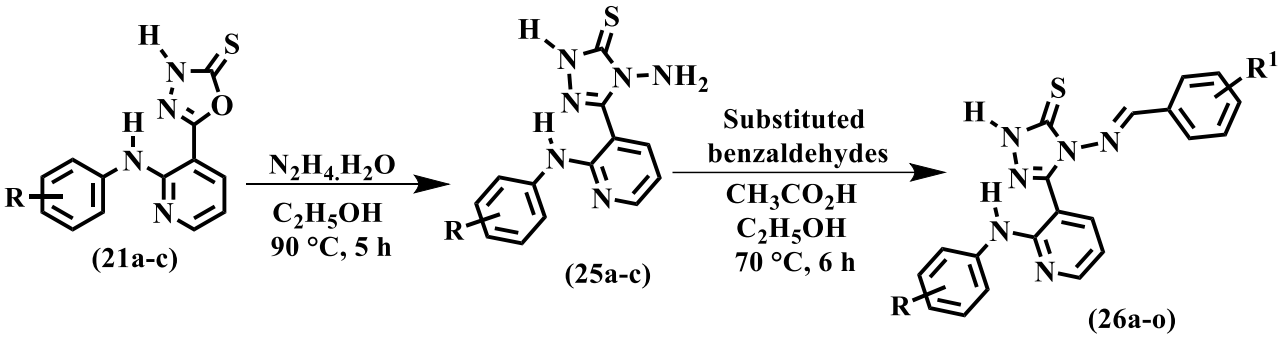


Where, R = 4-F, 3-Cl-4-F, 2-CH_3-5-NO_2; R^1 = 4-NO_2, 2,5-Cl_2, 2,4-Cl_2, 2-CH_3-5-NO_2, 2,4,5-Cl_3.

Scheme 4.1: Synthetic pathway for pyridine linked 1,2,3-triazol-4-yl-1,3,4-oxadiazole conjugates **(20a-o)**

Chapter 5: Synthesis and anticancer activity of the Schiff bases derived from 3-pyridyl substituted 1,2,4-triazole-3-thiones

This chapter explains the synthesis of some 4-[(arylidene)amino]-5-(2-[(aryl) amino]pyridin-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **(26a-o)** and their characterization, followed by preliminary anticancer evaluation by MTT assay against HeLa, A549 and MCF-7 cancer cell lines. The synthetic pathway for the target compounds **(26a-o)** is outlined in **Scheme 5.1**. The intermediates, 5-(2-arylaminopyridin-3-yl)-1,3,4-oxadiazole-2-thiones (**21a-c)** are synthesized from substituted anilines and 2-chloronicotinic acid as described in **Scheme 2.1** of **Chapter-2.** The intermediate thiones **(21a-c)** were then reacted with hydrazine hydrate in ethanol to obtain 4-amino-5-(2-arylaminopyridin-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **(25a-c)**. The intermediates **(25a-c)**, when reacted with various substituted aldehydes in ethanol under reflux conditions with a catalytic amount of acetic acid, afforded the 4-[(arylidene)amino]-5-(2-[(aryl)amino]pyridin-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **(26a-o).** The structures of the compounds are confirmed by elemental analysis, FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. Synthesized compounds were screened for their anticancer activity against HeLa, A549 and MCF-7 cancer cell lines by MTT assay. The compounds **26c**, **26e**, **26m**, **26n** and **26o** showed good anticancer activity against all the tested cancer cell lines**.** The *in silico* molecular docking studies of the synthesized derivatives showed good binding affinity towards the EGFR tyrosine kinase domain (PDB:1XKK).



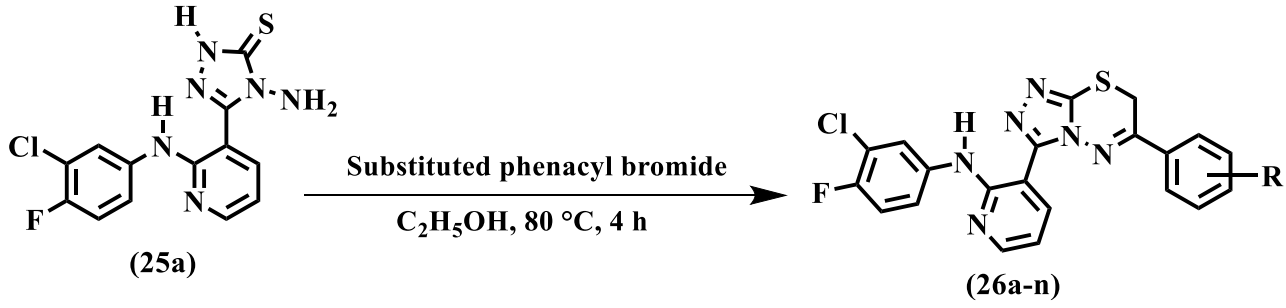
Where, **R** = 3-Cl-4-F, 4-F, 2-CH_3-5-NO_2; **R^1** = 4-NO_2, 4-OH, 4-Cl, 2,4-Cl_2, 4-OH-3-OCH_3

Scheme 5.1: Synthetic pathway for 4-[(arylidene)amino]-5-(2-[(aryl)amino]pyridin-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **(26a-o)**

Chapter 6: Synthesis and anticancer properties of [1,2,4]triazolo[3,4-*b*] [1,3,4] thiadiazines containing chloro-fluoroanilinopyridyl moiety

The synthetic protocol for synthesis of 6-aryl-3-(2-(3-chloro-4-fluoroanilino)pyridin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (**26a-n**) is shown in **Scheme 6.1.** Initially 4-amino-5-[2-{(3-chloro-4-fluorophenyl)amino}pyridin-3-yl]-2,4-dihydro-3*H*-1,2,4-triaz- ole-3-thione (**25a)** was synthesized form 3-chloro-4-fluoroaniline and 2-chloro-pyridine-3-carboxylic acid as described in **Scheme 5.1** of **Chapter-5**. The target compounds, 6-aryl-3-(2-(3-chloro-4-fluoroanilino)-pyridin-3-yl)-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazines **(26a-n)** were synthesized by the reaction of intermediate **(25a)** with various substituted phenacyl bromides in ethanol at reflux conditions. The formation of the compounds was confirmed on the basis of their elemental analysis, FTIR, ^{1}H /^{13}C NMR and mass spectroscopic data.

The synthesized compounds were screened for their anticancer activity against HeLa, MIA PaCa-2 and A549 cell lines. The compounds **26a**, **26b** and **26j** were identified as the most active compounds which were also screened against non-cancerous HEK293 cell. Results obtained from the study revealed that neither of the active compounds was harmful for non-cancerous HEK293 cells. The active compound **26b** was subjected to a Hoechst/PI double staining assay where it displayed induction of apoptosis by PI uptake in cervical cancer cell lines. The potency of compound **26b** to induce early and late apoptosis in cervical cancer cell lines was evaluated by Annexin/PI double staining assay. The compound **26b** was also subjected to foci formation assay where it displayed a potent reduction of colonies in HeLa cells.



Where, **R** = H; 4-F, 3-Cl; 4-Cl, 4-Br; 2,4-Cl_2; 4-CF_3, 3-NO_2, 4-NO_2, 4-OCF_3, 4-CH_3, 4-OCH_3, 4-OH, 3-(CO-NH_2)-4-OH.

Scheme 6.1: Synthetic pathway for the triazolothiadiazines containing chlorofluoroanilinopyridyl moiety **(26a-n)**

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List of Publications

A. Papers published/accepted/communicated in National/International Journals

1. **Vishwa B. Das**, Boja Poojary, Vinuta Kamat, Shanavaz Hamzad, Prabhat Suman, Synthesis, anticancer evaluation and molecular docking studies of 1,2,3-triazole embedded hydrazones as potential HER2 kinase inhibitors, *Rus. J. Org. Chem.* **2024**, *60*(3), 502-512.

2. **Vishwa B. Das,** Boja Poojary, Vinuta Kamat, Ankita Sharma, Rajdeep Chowdhury, Shanavaz Hamzad, Synthesis, *in silico* docking study and biological evaluation of S-alkylated 1,3,4-oxadiazole hybrids, *Rus. J. Org. Chem.* **2024,** 60 (5), 927-942.

3. Vinuta Kamat, Boja Poojary, Divyaraj Puthran, **Vishwa B. Das**, Banoth K. Kumar, Murugesan Sankaranarayan, Gauri Shetye, Rui Ma, Scott G. Franzblau, Suresh P. Nayak, Synthesis, antimycobacterial, cytotoxicity, anti-inflammatory, *in silico* studies and molecular dynamics of pyrazole-embedded thiazolidin-4-one hybrids, *Archiv der Pharmazie* **2023,** *356*(3), 2200444.

B. Details of the patent granted

1. Triazolothiadiazine derivatives as antineoplastic agents and their method of synthesis, **Vishwa B. Das**, Boja Poojary, Vinuta Kamat, Indian Patent, Patent Application No.: 202341037249, Patent No.: 499151, Date of grant: 15 Jan 2024.

C. Papers presented in National/International Conferences

1. **Vishwa B. Das,** Boja Poojary, Discovery of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)pyridin-2-amine derivatives as a new class of potent Anticancer agents. Presented at two days National Conference on “Impact of Chemistry and Biology to the Society and Industry” held during May 20-21, 2022 at Kuvempu University, Shivamogga, Karnataka.

2**. Vishwa B. Das,** Boja Poojary, Synthesis and anticancer activity of [1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)pyridin-2-amines. Presented at two day National Conference on “New Vistas in Chemistry” held during August 3-4, 2022 at Bangalore University, Bangalore.

Mr. Vishwa B. Das	Prof. Boja Poojary
(Research Scholar)	(Research Guide)